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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/394,020	09/10/1999	CARMEN V. PEPICELLI	HUIP-P01-032	3626

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EXAMINER

ANDRES, JANET L

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 09/16/2002

36

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/394,020

Applicant(s)

PEPICELLI ET AL.

Examiner

Janet L. Andres

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 June 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 and 22-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 and 22-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

RESPONSE TO AMENDMENT

1. Applicant's amendment filed 24 June 2002 is acknowledged. Claims 1-15 and 22-36 are pending in this application and are examined in light of the election of hedgehog antagonists. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections Withdrawn

2. The rejection of claims 1, 3, 25, and 26 under 35 U.S.C. 102(a) is withdrawn in response to Applicant's amendment limiting the claims to *in vivo* methods or methods involving the N-terminus of hedgehog.

3. The rejection of claims 6-15 and 29-32 under 35 U.S.C. 112, first paragraph, as lacking enablement and of claims 1-5 and 24-28 as lacking enablement commensurate with the scope of the claims is withdrawn in response to Applicant's presentation of the teachings of Katsuura et al.

Claim Rejections Maintained/New Grounds of Rejection

4. The rejection of claims 2 and 4 under 35 U.S.C. 103(a) as obvious over Fujita et al. is maintained for reasons of record in the office action of paper no. 33 and newly applied to claim 24, amended claims 1, 3, 5, 25, and 26, and new claim 36.

Applicant argues that the cited reference must teach each and every limitation of the claims, and that Fujita et al. does not teach *in vivo* inhibition. Applicant further argues that the teachings of Fujita et al. provides no reasonable expectation of success for the claimed methods.

Applicant's arguments have been fully considered but have not been found to be persuasive. The Examiner notes that the Fujita reference was provided by Applicant as evidence

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of enablement of Applicant's invention, but was published on September 18, 1997, before Applicant's earliest priority date of September 11, 1998. Further, MPEP § 2142 states that

[T]he prior art reference (or references when combined) must teach or suggest all the claim limitations.

not, as Applicant indicates, that the reference must teach each and every limitation. MPEP §

2143.01 further states:

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Additionally, MPEP §2144 states:

The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); ... *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

Thus, it is not necessary for Fujita et al. to explicitly teach *in vivo* methods. It would have been obvious to one of ordinary skill in the art, given the teachings of Fujita et al. that hedgehog antagonists can be used to inhibit the growth of cells derived from a human lung tumor, to use such inhibitors *in vivo*. The concept of treatment of cancer by inhibiting the

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growth of tumor cells would have been well known to one of ordinary skill at the time the invention was made, as would the use of *in vitro* systems to identify modulators useful *in vivo*.

One of ordinary skill would further, given the teachings of Fujita et al., have expected such an approach to be successful. MPEP §2164.02 teaches, regarding enablement of *in vivo* methods by *in vitro* testing,

An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a “working example” if that example “correlates” with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute “working examples.” In this regard, the issue of “correlation” is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating ...A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

Fujita et al. teaches that cells that were derived from a lung squamous carcinoma expressed SHH, whereas normal cells from the same patient did not (p. 662) and further teaches that lung squamous carcinoma lines express SHH and that their growth is inhibited by an anti-SHH antibody. One skilled in the art would thus accept the *in vitro* model as correlating with the *in vivo* condition, and would expect, based on these teachings, to be able to inhibit lung squamous carcinoma growth *in vivo*. Thus, one of skill in the art would accept the *in vitro* teachings of Fujita et al. as enabling for *in vivo* methods.

5. The rejection of claims 22, 23, 27, and 28 under 35 U.S.C. 103(a) as unpatentable over Fujita et al. in view of U.S. patent 6261786 is maintained for reasons of record in the office action of paper no. 33 and applied to new claims 34 and 35.

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Applicant argues as set forth above and further argues that the '786 patent fails to overcome the deficiency of Fujita et al. Since, however, Applicant's arguments with respect to Fujita et al. are not found to be persuasive, for the reasons set forth above, Applicant's arguments are similarly not found to be persuasive with respect to this rejection.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-15, 24-33, and 35 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are drawn to methods encompassing use of N-terminal portions of hedgehog proteins to inhibit hedgehog activity. As stated in the office action of paper no. 33, Fujita et al. teaches that the N-terminus is active. Applicant teaches the N-terminal extracellular region as "bioactive" (p. 4). What is required by the claims is that a sequence retain that part of the N-terminus that is required for binding to patched, but function as an inhibitor. No molecules having such an inhibitory activity are described in the specification. There is no description of the required structural features of such molecules, or of the regions that would be critical for the required function. Since these features are not disclosed, there is no way to determine what variations are required and what variations could be tolerated without altering the desired inhibitory function, or what fragments would possess the same defining characteristics. Therefore, applicant has not disclosed sufficient species or common structural features such that

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one skilled in the art would conclude that applicant was in possession of antagonistic hedgehog molecules retaining part of the N-terminus and thus of methods using them.

These claims were previously rejected under 35 U.S.C. 112, first paragraph, as lacking enablement or as lacking enablement commensurate with the scope of the claims. Applicant argues with respect to this rejection that it is routine to generate variants with loss of function. Applicant argues that the identification of variants with one set of characteristics does not suggest that mutations with other characteristics do not exist. Applicant points to references indicating that variants that can antagonize the function of hedgehog exist. Applicant provides the teachings of Katsuura et al. as evidence that such variants exist. Applicant further points to the large number of hedgehog mutations as indicating that some might possible be antagonistic.

While the teachings of Katsuura et al. are sufficient to indicate that antagonists containing part of the N-terminus exist, the specification as filed does not describe such antagonists. Applicant has provided no guidance beyond the mere presentation of hedgehog sequences to enable one of ordinary skill in the art to determine the nature and extent of changes that would be required to generate such inhibitors. There is no indication as to the regions that are important for binding or the regions that could be altered to generate an antagonist. There is nothing in the specification to indicate that Applicant was in possession of antagonistic hedgehogs such as the one taught by Katsuura et al. Although the specification outlines art-recognized procedures for producing muteins, this is not adequate guidance as to the nature of hedgehog antagonists that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. What is provided is thus the idea for an invention, and the invitation to experiment to implement this invention, not the invention itself.

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The teachings of Fujitsa et al. and of Nanni et al. further do not provide compensatory guidance. Neither the evidence that the N-terminus is the active region, nor the suggestion that antagonists might exist, is sufficient to describe molecules having the required characteristics. Neither of these references teaches the regions required for binding or the regions that must be altered to generate antagonists. Thus, one of skill in the art would not conclude, based on the teachings of the prior art and of Applicant's specification, that Applicant was in possession of such antagonists and of methods using them at the time the invention was filed.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564. The fax phone number for this group is (703) 872-9306 or (703) 872-9307 for after final communications.

Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

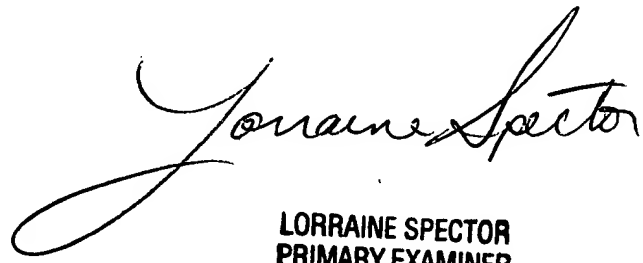
All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly

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set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet Andres, Ph.D.
September 12, 2002



LORRAINE SPECTOR
PRIMARY EXAMINER